# Impact of Smoking on Clinical Outcome and Recanalization After Intravenous Thrombolysis for Stroke

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Abstract: BACKGROUND AND PURPOSE: The impact of smoking on prognosis after stroke is controversial. We aimed to assess the relationship between smoking status and stroke outcome after intravenous thrombolysis in a large cohort study by adjusting for potential confounders and incorporating recanalization rates. METHODS: In a prospective observational multicenter study, we analyzed baseline and outcome data of consecutive patients with acute ischemic stroke treated with intravenous thrombolysis. Using uni- and multivariable modeling, we assessed whether smoking was associated with favorable outcome (modified Rankin Scale score of 0-1) and mortality. In addition, we also measured the occurrence of symptomatic intracranial hemorrhage and recanalization of middle cerebral artery. Patients reporting active cigarette use were classified as smokers. RESULTS: Of 1865 patients, 19.8% were smokers (n=369). They were younger (mean 63.5 versus 71.3 years), less often women (56% versus 72.1%), and suffered less often from hypertension (61.3% versus 70.1%) and atrial fibrillation (22.7% versus 35.6%) when compared with nonsmokers. Favorable outcome and 3-month mortality were in favor of smokers in unadjusted analyses (45.8% versus 39.5% and 9.3% versus 15.8%, respectively), whereas symptomatic intracranial hemorrhage was comparable in both cohorts. Smoking was not associated with clinical outcome and mortality after adjusting for confounders (odds ratio, 1.20; 95% confidence interval, 0.91-1.61; P=0.197 and odds ratio, 1.08; 95% confidence interval, 0.68-1.71; P=0.755, respectively). However, smoking still independently predicted recanalization of middle cerebral artery in multivariable analyses (odds ratio, 2.68; 95% confidence interval, 1.11-6.43; P=0.028). CONCLUSIONS: Our study suggests that good outcome in smokers is mainly related to differences in baseline characteristics and not to biological effects of smoking. The higher recanalization rates in smokers, however, call for further studies.

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# Impact of Smoking on Clinical Outcome and Recanalization after IV Thrombolysis for Stroke – Multicentre Cohort Study

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**Abstract**

Background: The impact of smoking on prognosis after stroke is controversial. We aimed to assess the relationship between smoking status and stroke outcome after intravenous thrombolysis (IVT) in a large cohort study by adjusting for potential confounders and incorporating recanalization rates.

Methods: In a prospective observational multicenter study, we analyzed baseline and outcome data of consecutive patients with acute ischemic stroke treated with IVT. Using uni- and multivariable modeling, we assessed whether smoking was associated with favorable outcome (modified Rankin Scale 0-1) and mortality. In addition, we also measured the occurrence of symptomatic intracranial hemorrhage (sICH) and recanalization of middle cerebral artery (MCA). Patients reporting active cigarette use were classified as smokers.

Results: Of 1865 patients, 19.8% were smokers (n=369). They were younger (mean 63.5 vs. 71.3 years), less often women (56% vs. 72.1%) and suffered less often from hypertension (61.3% vs. 70.1%) and atrial fibrillation (22.7% vs. 35.6%) as compared to nonsmokers. Favorable outcome and 3-month mortality were in favor of smokers in unadjusted analyses (45.8% vs. 39.5% and 9.3% vs. 15.8% and respectively), whereas sICH was comparable in both cohorts. Smoking was not associated with clinical outcome and mortality after adjusting for confounders (OR 1.20, 95% CI 0.91–1.61; p=0.197 and OR 1.08, 95% CI 0.68–1.71; p=0.755, respectively). However, smoking still independently predicted recanalization of MCA in multivariable analyses (OR 2.68, 95%CI 1.11–6.43; p=0.028).

Conclusion: Our study suggests that good outcome in smokers is mainly related to differences in baseline characteristics and not to biological effects of smoking. The higher recanalization rates in smokers, however, call for further studies.

## INTRODUCTION

Cigarette smoking is a well-known independent and modifiable risk factor for stroke in both men and women.[1, 2] Recent data indicate that about 20% of strokes are attributable to tobacco use, which may be even higher in younger patients with cryptogenic stroke.[3] Paradoxically, several studies suggested an association between smoking and good clinical outcome in patients treated with tissue plasminogen activator (tPA). This observation has been called “smoking paradox” in literature and was first described in patients with myocardial infarction.[4,5] The effect of smoking on stroke outcome after intravenous thrombolysis (IVT) is controversial, but recent studies reported higher rates of recanalization, lower risk for cerebral hemorrhage and better clinical outcomes in smokers.[6, 7, 8] We hypothesize that these observations may be rather caused by differences in clinical characteristics at baseline than by biological effects of smoking. We therefore conducted a large prospective study with in-depth analysis of clinical and radiological data to explore the association between smoking and outcome of ischemic stroke after IVT.

## METHODS

**Study design and setting.** As a joint initiative of four Swiss stroke centers (Berne, Basel, Zurich, Lausanne), we performed an observational multicenter cohort study to determine the impact of smoking status on stroke outcome after IVT. Detailed data on the number of consecutive patients and study period for each center are available as supplemental material (Table e-1).

**Participants.** Patients needed to meet the following 3 criteria for study inclusion: 1.) treatment with IVT (alteplase) for acute ischemic stroke according to the current guidelines of the European Stroke Organization,[9] 2.) knowledge about smoking status of the patient and 3.) availability of outcome data at 3 months. Patients were classified as smokers when they reported active cigarette use.

**Data sources and handling.** Data from individual patients were systematically and prospectively collected in each center by using a standardized form with pre-defined variables as applied in previous studies.[10] Compilation of completed forms from all centers and analyses of the pooled data were performed in the coordinating center in Berne, Switzerland. The study was approved by the ethics committee in Berne. The requirement for additional local ethical approval differed between participating centers and was obtained if required.

**Variables.** The following variables were prospectively collected in all participating centers: age, sex, smoking status and other vascular risk factors according to predefined criteria,[11] history of coronary artery disease, antithrombotic medication at stroke onset, initial stroke severity as assessed by the National Institutes of Health Stroke Scale (NIHSS) score,[12] stroke etiology according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria,[13] stroke onset-to-treatment time as well as blood pressure and blood glucose level obtained at admission. Patency of extra- and intracranial arteries at baseline was assessed by the initial CT or MR angiography in a subgroup of patients. All patients treated with IVT were admitted to intermediate or intensive care units for at least 24 hours. All patients underwent brain imaging with computed tomography or magnetic resonance imaging 24 to 48 hours after IVT and in any case of clinical deterioration.

**Assessment of outcomes.** Clinical outcomes were assessed during outpatient visits using the modified Rankin Scale (mRS) score at 3 months.[14] Main outcome measures in this study were (i) favorable outcome (defined as mRS 0 or 1), (ii) death within 3 months and (iii) symptomatic intracerebral hemorrhage (sICH) according to the definition of the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST).[15] In addition, we also used the thrombolysis in cerebral infarction (TICI) score on follow-up angiography 24 hours after IVT to evaluate arterial recanalization in a subgroup of patients with vessel occlusion of the M1 segment in middle cerebral artery (MCA-M1).[16] The TICI scores of 2b

(partial reperfusion of >50%) and 3 (complete reperfusion) were defined as successful recanalization.[17]

**Statistical methods.** We compared demographic and baseline characteristics between smokers and non-smokers by using Fisher exact test for dichotomous variables and Mann-Whitney U test for continuous variables in univariate analyses. The independent effect of smoking status on outcome was assessed in a multivariable logistic regression model. Any variable with $p < 0.15$ in the univariate analysis was entered into the regression model. Age and baseline NIHSS score were entered as mandatory into the model because they have been proven to be independent predictors of clinical outcome after stroke.[18] We additionally performed multivariable logistic regression analyses including clinically relevant outcome predictors (age, gender, NIHSS and time to treatment for favorable outcome; age, gender and NIHSS for mortality; age, gender, NIHSS, systolic blood pressure, baseline glucose and antithrombotic treatment at baseline for sICH).[7, 18-22] The level of statistical significance was set to 0.05. Statistical analyses were conducted by using the statistical software R (version 3.1.2 - R Core Team [2014]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

A total of 2237 patients were treated with IVT within study period. Data on smoking status were not available in 301 patients and outcome data were missing in 71 patients. Thus, 1865 patients were eligible for this study. Of these, 369 (19.8%) were current smokers. The main baseline characteristics of the 2 groups are detailed in Table 1. As compared to non-smokers, smokers were more often male (72.1% vs. 56.0%, p<0.001), were younger (mean 63.5 vs. 71.3 years, p<0.001) and suffered less often from arterial hypertension (61.3% vs. 70.1%, p=0.001) and atrial fibrillation (22.7% vs. 35.6%, p<0.001). Stroke etiology differed between the 2 groups (p<0.001) as cardioembolic stroke was more common among non-smokers than smokers (48.2% vs. 35%), whereas large artery atherosclerosis was more common among smokers than non-smokers (17.4% vs. 11.6%). However, stroke severity indicated by baseline NIHSS score was comparable between the groups (mean 11.0 vs. 11.4, p=0.417). Non-smoking patients were more often treated with antithrombotic drugs at baseline (46.7% vs. 39%, p=0.008). Vessel occlusion was documented in 959 (51.4%) patients. Imaging at baseline showed arterial occlusion in 174 of 369 (47.1%) smokers and in 785 of 1496 (52.4%) non-smokers. Extracranial occlusion of internal carotid artery (ICA) occurred more frequently in smokers (21.8% vs. 12.6%), whereas intracranial occlusions in anterior cerebral circulation such as carotid-T (4.6% vs. 4.3%) or MCA-M1 (31% vs. 35.3%) were comparable with non-smokers.

Clinical outcomes are summarized in Table 2. At 3 months, smokers had higher rates of favorable outcome (45.8% vs. 39.5%, p=0.029) and lower mortality rates (9.8% vs. 15.8%, p=0.003) than non-smokers, whereas the rates of sICH did not significantly differ between the groups (3.0% vs. 3.8%, p=0.536).

For multivariable regression analyses, the following covariates were entered into the model: age, gender, baseline NIHSS, atrial fibrillation, arterial hypertension, baseline use of antithrombotics, baseline blood glucose and stroke etiology according to TOAST classification (Tables 2 and e-2). After adjusting for these covariates, smoking status was not

associated with favorable outcome (Odds ratio (OR) 1.20, 95% confidence interval (95% CI) 0.91–1.61; p=0.197), mortality (OR 1.08, 95% CI 0.68–1.71; p=0.755) or sICH (OR 1.08, 95% CI 0.52–2.26; p=0.833).

In patients with occlusion of MCA-M1, radiological recanalization was significantly more often documented in smokers than in non-smokers (72.7% vs. 56%, p=0.045). After multivariable adjustment, smoking was still associated with recanalization (OR 2.68, 95% CI 1.11–6.43; p=0.028), together with NIHSS (p=0.045) and cardioembolic stroke etiology (p=0.002).

In addition, we performed a sensitivity analysis by running the same multivariable regression model without adjustment for the NIHSS score. However, the overall conclusion did not change as smoking was still associated with recanalization (OR 2.24, 95% CI 1.03-4.88; p=0.043), but not with favorable outcome (OR 1.15, 95% CI 0.88-1.48; p=0.307), mortality (OR 0.99, 95% CI 0.65-1.52; p=0.970) or sICH (OR 1.07, 95% CI 0.52 -2.22; p=0.852).

Results of additional outcome analyses including clinically relevant predictors are summarized in Table e-3. Age and NIHSS again independently predicted all clinical outcomes (favorable outcome, mortality and sICH), whereas no association was observed between smoking and clinical outcome.

## DISCUSSION

This large multi-center cohort study on 1865 patients with acute ischemic stroke suggests that good outcome in smokers after IVT as shown in unadjusted analyses is probably related to differences in baseline characteristics as multivariable analyses revealed no significant association between smoking status and clinical endpoints (favorable outcome, mortality, sICH).

Considering differences in baseline characteristics is crucial for discussion of “smoking paradox” in stroke patients. In line with the literature, smokers were significantly younger, more likely to be male and suffered less often from atrial fibrillation than non-smokers.[23, 24] Accordingly, stroke due to cardioembolism occurred significantly more often among non-smokers than in smokers. It has been shown, that older age is one of the most important and independent predictors for death and unfavorable outcome in stroke.[25, 26] Furthermore, female gender has been reported to correlate with worse outcome after stroke.[26, 27, 28] Of note, the proportion of male gender was higher in smokers than in counterpart. Cardioembolic stroke due to atrial fibrillation is known to be associated with large territorial infarcts, longer and tight thrombus formation, higher risk of hemorrhagic transformation and unfavorable clinical outcomes.[29-33] In line with this, noncardioembolic strokes may be independently related to good outcome in smoking patients treated with IVT.[34] Thus, these imbalances at stroke onset may explain the impression of favorable outcome in smokers (“smoking paradox”). Multivariable analyses in our study revealed that clinical recovery and mortality was not related to smoking status, but age, stroke severity (measured by using NIHSS) and blood glucose. These findings are in line with literature.[20, 35, 36] Furthermore, the risk of sICH was comparable in smokers and in non-smokers (both in univariate and multivariable analyses), whereas few studies suggested lower risk of sICH in smokers treated with tPA.[7, 34]

Our findings are in line with other IVT studies who failed to demonstrate an independent association of smoking status with 3-month outcome.[24, 37-39] Only one study showed an

independent relation between current smoking and favorable short-term outcome, but outcomes were assessed at 1 week after thrombolysis or earlier.[8] In addition, the sample size of smokers was rather low (n=94).[8]

A subgroup analysis in patients with MCA-M1 occlusion showed higher recanalization rates in smokers. The association with smoking remained still significant after multivariable adjustment. Our findings fit to previously published studies showing that smoking was associated with recanalization and reperfusion in smokers treated with tPA for ischemic stroke.[34, 40] Two reasons might explain our observation. First, arterial occlusions in smokers may be rather thrombogenic because smoking is associated with a hypercoagulable state mediated by increased hematocrit and fibrin-rich clots, higher fibrinogen levels and impaired endogenous fibrinolytic capacity.[41, 42] This may explain the better response to thrombolytic treatment in smokers with higher rates of recanalization. In line with this, higher rates of arterial recanalization have been reported in smoking patients with acute myocardial infarction undergoing systemic thrombolysis.[5, 43-45] On the other hand, arterial occlusion in non-smokers may be more frequently due to rupture or ulceration of atheromatous plaque with no or little response to thrombolytic treatment. Second, smoking has also been associated with increased plasma levels of carbon monoxide and episodic hypoxia[46] which could lead to ischemic preconditioning and may trigger adaptive cellular responses to ischemia.[47, 48] However, the results on arterial recanalization should be interpreted with caution as data originate from subgroup analyses with a low number of patients in our study (n=331) and former studies (n=79).[37] In accordance with our study, NIHSS on admission but not smoking status was an independent predictor of functional recovery.[37] The hazardous effect of cigarette smoking is reflected by the occurrence of stroke many years earlier than in non-smokers.

The main strength of our study is the large cohort size and multi-center design, which allows adjustment for potential confounders. This is to our best knowledge the largest outcome study assessing relationship between IVT and smoking status in 1865 stroke patients as

compared to former studies in Caucasian patients (range 148 to 399, mean 299).[38 8, 24] Thus, the markedly larger sample size of our study will result in better statistical power than in previous studies. Furthermore, data quality was high as both clinical and radiological data were systematically and prospectively collected at baseline and during 3-month follow-up.

This study has also some limitations. First, this was an observational, non-randomized study with a higher risk of bias which may not be completely removed though the multivariable model. We did not systematically record the quantity of smoking exposure, leading to high heterogeneity in our smoking cohort and prohibiting a differentiation of heavy vs. mild smokers and to assess a dose-response relationship between smoking and outcome. Lacking data on earlier smoking status, we were not able to compare outcomes in current smokers vs. former smokers. Despite covariate adjustments, there may be hidden confounders we did not consider in our study such as differences in rehabilitation, socio-economic status, caregiver support, medical complications and recurrent strokes within 3 months after event. Furthermore, data on occlusion and recanalization was only available in a subgroup of patients accounting for 14% of the entire cohort. Thus, data on recanalization need to be interpreted cautiously given the small sample size and the large number of covariates adjusted for. Finally, we did not measure changes in smoking habits (e.g. cessation) after stroke, which may also have influenced the 3-month outcomes.

## Conclusion

Our data indicate that smoking has no beneficial effect on stroke outcome after IVT and contradict the hypothesis of a smoking paradox in stroke. The apparently good outcome in smokers was largely related to younger age and other differences in baseline characteristics. Although the odds for arterial recanalization after IVT might be higher in smokers due to different pathophysiologic mechanisms, the earlier occurrence of stroke in the lifetime of smokers offsets a potential benefit in recanalization.

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Table 1. Baseline Characteristics of Patients According to Smoking Status

| | Smokers (n=369) | Non Smokers (n=1496) | Risk difference (95% CI) | *P* Value |
|---|---|---|---|---|
| Male sex (%) | 266/369 (72.1) | 838/1496 (56.0) | 16.1% (10.9% to 21.3%) | < 0.001 |
| Mean age ± SD (years) | 63.5 ± 12.6 | 71.3 ± 15.8 | -7.8 (-9.3 to -6.3) | < 0.001 |
| Hypertension (%) | 225/367 (61.3) | 1047/1493 (70.1) | -8.8% (-14.3% to -3.3%) | 0.001 |
| Diabetes mellitus (%) | 70/368 (19.0) | 239/1487 (16.1) | 2.9% (-1.5% to 7.4%) | 0.184 |
| Dyslipidemia (%) | 189/350 (54.0) | 721/1449 (49.8) | 4.2% (-1.6% to 10.1%) | 0.171 |
| Antiplatelet medication at stroke onset (%) | 141/362 (39.0) | 694/1485 (46.7) | -7.7% (-13.4% to -2.2%) | 0.008 |
| Coronary heart disease (%) | 73/368 (19.8) | 297/1481 (20.1) | -0.3% (-4.7% to 4.3%) | 1.0 |
| Atrial fibrillation (%) | 80/352 (22.7) | 506/1423 (35.6) | -12.9% (-17.9% to -7.9%) | <0.001 |
| Mean NIHSS score ± SD | 11.0 ± 6.42 | 11.4 ± 6.7 | -0.4 (-1.1 to 0.4) | 0.417 |
| Time to treatment ± SD | 159.3 ± 49.2 | 160.1 ± 50.5 | -0.8 (-6.4 to 5.0) | 0.687 |
| Mean systolic blood pressure ± SD (mm Hg) | 156.8 ± 27.3 | 157.4 ± 26.6 | -0.6 (-3.8 to 2.6) | 0.406 |
| Mean diastolic blood pressure ± SD (mm Hg) | 87.7 ± 17.5 | 86.4 ± 18.6 | 1.3 (-0.8 to 3.4) | 0.187 |
| Mean blood glucose ± SD (mmol/L) | 7.07 ± 2.71 | 7.01 ± 2.22 | 0.1 (-0.2 to 0.4) | 0.108 |
| Cause of stroke | | | | <0.001 |
| Large artery atherosclerosis (%) | 62/357 (17.4) | 165/1419 (11.6) | 5.7% (1.5% to 10.0%) | |
| Cardiac embolism (%) | 125/357 (35.0) | 684/1419 (48.2) | -13.2% (-18.8% to -7.6%) | |
| Small artery disease (%) | 28/357 (7.8) | 62/1419 (4.4) | 3.5% (0.5% to 6.5%) | |
| Other determined etiology (%) | 27/357 (7.6) | 91/1419 (6.4) | 1.2% (-1.9% to 4.2%) | |
| Undetermined etiology (%) | 115/357 (32.2) | 417/1419 (29.4) | 2.8% (-2.6% to 8.2%) | |

NIHSS denotes National Institutes of Stroke Scale, SD standard deviation and CI confidence interval

Table 2. Outcomes after Intravenous Thrombolysis According to Smoking Status

| | **Smokers [n/N (%)]** | **Non-Smokers [n/N (%)]** | ***P* Value Unadjusted [OR, 95% CI]** | ***P* Value Adjusted * [OR, 95% CI]** |
|---|---|---|---|---|
| **Favorable Outcome** | 169/369 (45.8) | 591/1496 (39.5) | 0.029 [1.30, 95% CI 1.02 - 1.64] | 0.197 [1.20, 95% CI 0.91 - 1.61] |
| **Mortality** | 36/369 (9.8) | 237/1496 (15.8) | 0.003 [0.57, 95% CI 0.38 - 0.84] | 0.755 [1.08, 95% CI 0.68 - 1.71] |
| **Symptomatic ICH** | 11/365 (3.0) | 56/1471 (3.8) | 0.536 [0.79, 95% CI 0.37 - 1.53] | 0.833 [1.08, 95% CI 0.52 - 2.26] |
| **Recanalization of MCA** | 32/44 (72.7) | 121/216 (56.0) | 0.045 [2.09, 95% CI 0.98 - 4.70] | 0.028 [2.68, 95% CI 1.11 - 6.43] |

ICH denotes intracranial hemorrhage, MCA middle cerebral artery (M1 segment), OR odds ratio and CI confidence interval

* adjusted for age, gender, stroke severity, atrial fibrillation, arterial hypertension, baseline use of antithrombotics, baseline blood glucose, stroke etiology and smoking status